# IDS REFERENCES

☐ FOR

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**DECLARATION OF DR. YITZHAK PILPEL UNDER 37 C.F.R. § 1.132**

I, Yitzhak Pilpel (Ph.D.), hereby declare as follows:

1. I am currently employed as a faculty member at the Department of Molecular Genetics of the Weizmann Institute, Israel. A true and correct copy of my *Curriculum Vitae* is attached to this declaration as Exhibit A. I am an author of [34 peer-reviewed scientific publications, of which 2 are related to microRNAs ("miRNAs"). I have supervised at least 3 experiments relating to microRNAs including computational mining of the mammalian microRNA repertoire, and experimental analyses of the regulatory agents controlling microRNAs.

2. A nucleic acid sequence of length 18-25 (endogenous or synthetic), which is predicted by a microRNA target algorithm, to bind to the 3' UTR of a mRNA in a manner characteristic of mirRNA:mRNA binding, when co-expressed with the target mRNA (such as in an in vitro reporter gene assay), is likely to inhibit expression of the protein encoded by that mRNA.

3. Binding of microRNA to mRNA is characterized by **a)** 5'-end 'seed '(full complementary between the first 1-8 base pairs of the 5' of a mir and its target), conserved, often flanked by adenosines; **b)** Compensatory 3'-end in cases in which there is insufficient base-pairing of the microRNA 5' seed; and **c)** Multiple binding sites on the same mRNA targets which are not obligatory but enhance the binding effect on target repression. The above charectharistics were described by various publications, including: Lai and Starck (Nat Genet, 2002; PloS Biol., 2003), Doench and Sharp (Genes Dev., 2004), Lai (Genome Biol., 2004), Vella et. al. (Chem. Biol., 2004) and Brennecke et. al. (PLoS Biol., 2005)

4. The effectiveness of microRNA targets prediction algorithms that are based on the above characteristics has been described by numerous studies. As an example, Lewis et. al. (Cell 2003), reported a microRNA target prediction algorithm, TargetScan, which is based on the above mentioned characteristics, and have biologically validated 11 out of 15 predicted targets tested, estimating the algorithm's false positive rate to be between 22 and 31 percent. Another algorithm, called miRanda (Enright et. al., Genome Biol. 2003), correctly recovered 9 out of 10 biologically validated targets, with an estimated 24-39% false positive rate.

5. **Table A** below provides a list of characteristic nucleic-acid-sequences:mRNA bindings, taken from Rosetta Genomics' patent applications. These nucleic acid sequences exhibit the characteristics of miRNA:mRNA bindings described above, and therefore are likely to inhibit their respective targets where co-expressed (such as in an in vitro reporter gene assay). Indeed, nearly all of the listed bindings are similarly detected by the above mentioned TargetScan algorithm, and half of them are further either detected by the miRanda algorithm, and/or are evolutionarily conserved.

6. It is my opinion that each sequence in column A would likely inhibit the expression of a protein encoded by the target gene in column B in view of the characteristics of miRNA:mRNA binding described above in paragraph 3.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent application relying on this declaration or any patent issuing thereon.

Dated 1/09/08 -- By Itzchi Pilpel

**Exhibit A**

CV

**Table A:**

| Column A<br>Nucleic acid sequence | Column B<br>Nucleic-acid:target-gene binding site scheme<br>(in grey : the seed region at 5' of the binding nucleic acid) | Column C<br>Supportive data from patent application regarding nucleic-acid's and target-gene's utility | Column D<br>Supportive data from current literature & Rosetta Genomics studies | E<br>TargetScan[1] | F<br>Targett Conservation[2] | G<br>miRanda[3] |
|---|---|---|---|---|---|---|
| **TAGGTAGTTTCCTGTTGTTGGG**<br><br>Sanger name: hsa-miR-196b<br><br>(Filed in US patent application no. 10/707,147) | **Nucleic-acid**<br>CCT TG-<br>5' TAGGTAGTTT GT TTGGG 3'<br>3' ATCCATCAAA CA AACCC 5'<br>AAT CCA<br>**Target gene**<br><br>17/22 complementary base pairs<br><br>Table 4 (lines 111217-111221)<br>Target/seqID: LHFPL2/6663<br>Nucleic acid seqID/GAM: 354/7553 | **Pages 180513-51163 paragraphs 51160-51163**<br>"Another function of GAM7553 is therefore inhibition of MBNL2 (Accession NP_005748.1) . Accordingly, utilities of GAM7553 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBNL2. MBNL2 (Accession NP_659002.1) is another GAM7553 target gene, herein designated TARGET GENE. MBNL2 BINDING SITE is a target binding site found in the 3' untranslated region of multiple transcripts of mRNA encoded by MBNL2, corresponding to a target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig.8. Table 4 illustrates the complementarity of the nucleotide sequences of MBNL2 BINDING SITE, designated SEQ ID:5708, to the nucleotide sequence of GAM7553 RNA, herein designated GAM RNA, also designated SEQ ID:354 . Another function of GAM7553 is therefore inhibition of MBNL2 (Accession NP_659002.1) . Accordingly, utilities of GAM7553 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBNL2." | | + | + | + |
| **CTAGACTGAAGCTCCTTGAGGA**<br><br>Sanger name: hsa-miR-151<br><br>(Filed in US patent application no. 10/708,204) | **Nucleic-acid**<br>C- T A<br>5' CTAGACTGAAG TCC TG GG 3'<br>3' GGTCTGACTTC AGG AC CC 5'<br>TC T -<br>**Target gene**<br><br>18/22 complementary base pairs<br><br>Table 7 (lines 1488-1492)<br>Target/seqID: SERPINA3/5331<br>Nucleic acid seqID/GAM:15/1032 | **Table 8 (lines 7222-7243)**<br>" Another function of GAM1032 is therefore inhibition of SERPINA3, a GAM1032 target gene which is a member of the serpin family of serine protease inhibitors. and therefore is associated with Alzheimer. Accordingly, utilities of GAM1032 include diagnosis, prevention and treatment of Alzheimer, and of other diseases and clinical conditions associated with SERPINA3.The function of SERPINA3 has been established by previous studies. Alpha- 1-antichymotrypsin is a plasma protease inhibitor synthesized in the liver. It is a single glycopeptide chain of about 68,000 daltons and belongs to the class of serine protease inhibitors. In man, the normal serum level is about one-tenth that of alpha- 1- antitrypsin (PI; 107400), with which it shares nucleic acid and protein sequence homology (Chandra et al. 1983). Both are major acute phase reactants: their concentrations in plasma increase in response to trauma, surgery, and infection. Antithrombin III, which also is structurally similar to alpha- 1- antitrypsin, shows less sequence homology to antichymotrypsin and is not an acute phase reactant. Kelsey et al. (1988) cloned and analyzed the AACT gene, partly because of the possibility that genetic variation in other protease inhibitors may influence the prognosis in AAT deficiency. They isolated the AACT gene on a series of cosmid clones, with restriction mapping of about 70 kb around the gene. " | a. SERPINA3 mRNA levels are increased in schizophrenia Saetre et. al. (Saetre et. al. BMC Psychiatry. 2007)<br><br>b. Rosetta Genomics: has-mir-151 is highly expressed in a variety of tissues. | | | |
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| **AAAGTGCTTCTCTTTGGTGGGT**<br><br>Sanger name hsa-miR-520d<br><br>(Filed in US patent application no. 10/708,951) | **Nucleic-acid**<br>-- - - ------<br>5′ C AC A AGCACTTT 3′<br>3′ G TG T TCGTGAAA 5′<br>TG G G TTCTCT<br><br>**Nucleic acid**<br><br>21/22 complementary base pairs<br><br>Table 7 (lines 26274 - 26282)<br>Target/seqID: MICA/23420,24238<br>Nucleic acid seqID/GAM:1485/ 338499 | **Table 8 (80406 – 80439):**<br>"A function of GAM338499 is therefore inhibition of MICA, a GAM338499 human target gene which encodes for a protein that binds to the receptors on T-cells and NK cells, activating cytolytic responses, induced by oxidative stress and bacteria. MICA is associated with Mycobacterium avium subsp. Paratuberculosi , Mycobacterium bovis subsp bovis AF2122/97 and Mycobacterium tuberculosis CDC1551 infections, and therefore GAM338499 is associated with the abovementioned infections, as part of a host response mechanism. Accordingly, utilities of GAM338499 include diagnosis, prevention and treatment of Mycobacterium avium subsp. paratuberculosis, Mycobacterium bovis subsp bovis AF2122/97 and Mycobacterium tuberculosis CDC1551 infections and associated clinical conditions. The function of MICA and its association with various diseases and clinical conditions has been eestablished by previous studies, as described hereinabove with reference to GAM336293." | *a.* MICA is a target gene of hsa-miR-373 which has the same 'seed' as hsa-miR-520d. (Lim et al., 2005)<br><br>*b.* Rosetta Genomics: the expression of miR-520d is significantly decreased in lung cancer | + | | |
| **AGAAAGTGCTTCCCTTTGGTGA**<br><br>Sanger name: hsa-mir-527* <br><br>(Filed in US patent application no. 10/708,953) | **Target gene**<br>-- - -- CCCT-<br>5′ AC A G CACTTTCT 3′<br>3′ TG T C GTGAAAGA 5′<br>AG G TT CCTTC<br><br>**Nucleic-acid**<br><br>12/22 complementary base pairs<br><br>Table 7(lines 100-105)<br>Target/seqID:SRY/1734694<br>Nucleic acid seqID/GAM:8385/345997 | **Table 8 (lines 4903950-4903970)**<br>"Sex- determining regioo Y (testis determining factor) (SRY, Accession NM_003140) is another GAM345997 target gene encoded by the human genome. SRY BINDING SITE is a human target binding site found in the 3' untranslated region of mRNA encoded by SRY, corresponding to a target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig.8. Nucleotide sequences of SRY BINDING SITE, and secondary structure complementarity to the nucleotide sequence of GAM345997 RNA are set forth in Tables 6-7, hereby incorporated herein Another function of GAM345997 is therefore inhibition of SRY, a GAM345997 human target gene which is associated with male sex determination. SRY is associated with Turner Syndrome disease, and therefore GAM345997 is associated with the abovementioned disease. Accordingly, utilities of GAM345997 and of other diseases and clinical conditions associated with SRY." | Rosetta Genomics: has-mir-527* is expressed in a variety of tissues. | + | | |
| **CAGCAGCACACTGTGGTTTGTA**<br><br>Sanger name: hsa-miR-497<br><br>(Filed in US patent application no. 10/709,691) | **Target gene**<br>-- -- -----<br>5′ CA CCA TGCTGCTG 3′<br>3′ GT GGT ACGACGAC 5′<br>AT TT GTCAC<br><br>**Nucleic-acid**<br><br>13/22 complementary base pairs<br><br>Table 7_A (lines 15144-15148)<br>Target/seqID:MGAT5/1810388<br>Nucleic acid seqID/GAM:348/353678 | **Table 8_a (lines 34080-34165)**<br>"Another function of GAM353678 is to inhibit MGAT5, a GAM353678 human target gene which encodes an enzyme that catalyzes beta 1-6 branching on N-linked carbohydrates. MGAT5 is associated with Salmonella typhimurium LT/2 infection, and therefore GAM35 3678 is associated with the abovementioned infection, as part of a host response mechanism. Accordingly, the utilities of GA M353678 include the diagnosis, prevention and treatment of Sal monella typhimurium LT2 infection and associated clinical conditions. The function of MGAT5 and its association with various diseases and clinical conditions has been established by previous studies, as described hereinabove with reference to GAM3451. " | Rosetta Genomics: mir-497 is highly expressed in brain, prostate, kidney and thymus. | + | | |
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| **TCACCAGAATGCTAGTTTGTAGAG**<br><br>Sanger name:hcmv-miR UL22A*<br><br>(Filed in US patent application no. 10/707,003) | **Nucleic-acid**<br>A CTA<br>5′ TCACCAGA TG GTTTG 3′<br>3′ AGTGGTTT AC CAAAC 5′<br>_ AAC<br>**Target gene**<br><br>14/24 complementary base pairs<br><br>Table 2 (Lines 54353-54357)<br>Target/seqID:AKAP7/11253<br>Nucleic acid seqID/GAM:3588/877 | **Pages 17094-17095, paragraph 33328-33329**<br><br>"A Kinase (PRKA) Anchor Protein 7 (AKAP7, Accession NM_004842) is another VGAM877 host target gene. AKAP7 BINDING SITE1 through AKAP7 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AKAP7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP7 BINDING SITE1 through AKAP7 BINDING SITE3, designated SEQ ID:11253, SEQ ID:18516 and SEQ ID:28906 respectively, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.Another function of VGAM877 is therefore inhibition of A Kinase (PRKA) Anchor Protein 7 (AKAP7, Accession NM_004842). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP7." | | + | | |
| **CGCACCACTAGTCACCAGGTGT**<br><br>Sanger name: ebv-miR-BART3<br><br>Filed in US patent application no.10/708,952 | **Target gene**<br>--- GA GTTG -<br>5′ CCTGGTGA A GTGGTG G 3′<br>3′ GGACCACT T CACCAC C 5′<br>TGT GA ---- G<br><br>**Nucleic-acid**<br><br>16/22 complementary base pairs<br><br>Table 7(Lines 844212 - 844215)<br>Target/seqID:NP_0399 06.1<br>Nucleic acid seqID/GAM:14051/351387 | **Table 8 lines 2025078-2025094**<br><br>"NP_039906.1 gene BINDING SITE1 and NP_039906.1 gene BINDING SITE2 are viral target binding sites found in untranslated regions of mRNA encoded by NP_039906.1 gene, corresponding to target binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig.1. Nucleotide sequences of NP_039906.1 gene BINDING SITE1 and NP_039906.1 gene BINDING SITE2, and secondary structure complementarity to the nucleotide sequence of GAM351387 RNA are set forth in Tables 6-7, hereby incorporated herein.A function of GAM351387 is therefore inhibition of NP_039906.1 gene, a GAM351387 viral target gene which is associated with Human herpesvirus 4 (Epstein-Barr virus) infection, as part of an internal viral regulation mechanism. Accordingly, utilities of GAM351387 include diagnosis, prevention and treatment of Human herpesvirus 4 (Epstein - Barr virus) infections and associated clinical conditions." | | | | |
| **TCTCTGGTTAGACCAGATCTGAGC*** <br><br>(Filed in US patent application no.10/604,945) | **Nucleic-acid**<br>CCAGA _<br>5′ TCTGGTTAGA TCT GAGC 3′<br>3′ AGACCAATCT AGA CTCG 5′<br>A____ T<br>**Target gene**<br><br>17/22 complementary base pairs<br><br>Table 2(Lines 35003-35007)<br>Target/seqID:SF3B3/ 29681<br>Nucleic acid seqID/GAM:5264/2191 | The utilities of the nucleic acid are depicted in details in Pages 4018-4021, paragraphs 30621-30626.<br>The below citation taken from the paragraphs mentioned above:<br>"It is yet further appreciated that a function of VGAM2191 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM2191include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1.<br>Specific functions, and accordingly utilities, of VGAM2191 correlate with, and may be deduced from, the identity of the host target genes which VGAM2191 binds and inhibits, and the function of these host target genes, as elaborated herein below." | Rosetta Genomics biologically validated this mir. | + | + | + |

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| **TGCTATTTCGGCTGCCAGAGTGTC***<br><br>(Filed in US patent application no.10/604,943) | **Nucleic-acid**<br>C CA___<br>5' TGCTATTT GGCTGC GAGTGT 3'<br>3' ACGATAAA CCGACG TTCACA 5'<br>_ CCGAC<br>**Target gene**<br>20/22 complementary base pairs<br><br>Table 2(Lines 7383-7387)<br>Target/seqID:INHBA/904<br>Nucleic acid seqID/GAM:480/145 | **Page 830 paragraphs 1993**<br>"It is yet further appreciated that a function of VGAM145 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM145 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM145 correlate with, and may be deduced from, the identity of the host target genes which VGAM145 binds and inhibits, and the function of these host target genes, as elaborated herein below."<br>Paragraph 5315 per the VGR386 utility (which encodes an 'operon-like' cluster of novel viral micro RNA-like gene, including VGAM 145)<br>"It is appreciated that a function of VGR389 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR389 gene include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGR389 gene correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the 'operon-like' cluster of VGR389 gene:VGAM142 host target protein, VGAM143 host target protein, VGAM144 host target protein, VGAM145 host target protein,VGAM146 host target protein and VGAM147 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN. The function of these host target genes is elaborated hereinabove with reference to VGAM142, VGAM143, VGAM144, VGAM145, VGAM146 and VGAM147.Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 390 (VGR390) viral gene, which encodes an 'operon-like' cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art." | Rosetta Genomics validated this nucleic acid by Real Time PCR. | + | + | |
| **TCTATGTTCCTCGTTTCCTGTATT***<br><br>(Filed in US patent application no.10/604,943) | **Nucleic-acid**<br>C C<br>5' TCTATGTT CT GTTTCC 3'<br>3' AGATACAA GA CAAAGG 5'<br>A _<br>**Target gene**<br>16/22 complementary base pairs<br><br>Table 2(Lines 7428-7432)<br>Target/seqID:ZNF36/3627<br>Nucleic acid seqID/GAM:482/147 | **Page 842 paragraphs 2021**<br>"It is yet further appreciated that a function of VGAM147 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM147 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM147 correlate with, and may be deduced from, the identity of the host target genes which VGAM147 binds and inhibits, and the function of these host target genes, as elaborated herein below."<br>Paragraph 5315 per the VGR386 utility (which encodes an 'operon-like' cluster of novel viral micro RNA-like gene, including VGAM 147)<br>"It is appreciated that a function of VGR389 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR389 gene include diagnosis, prevention and treatment of viral infection by Vaccinia Virus.Specific functions, and accordingly utilities, of VGR389 gene correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised | Rosetta Genomics validated this mir by Real Time PCR. | + | | |

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| | | in the `operon-like` cluster of VGR389 gene:VGAM142 host target protein, VGAM143 host target protein, VGAM144 host target protein, VGAM145 host target protein,VGAM146 host target protein and VGAM147 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN. The function of these host target genes is elaborated hereinabove with reference to VGAM142, VGAM143, VGAM144, VGAM145, VGAM146 and VGAM147.Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 390(VGR390) viral gene, which encodes an `operon-like` cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art." | | | | |
| **CGCCTTTATTTCCACATTAGATGG*** (Filed in US patent application no.10/604,943) | **Nucleic-acid**<br>C TA<br>5′ GCCTTTATT TCCA AT GATGG 3′<br>3′ CGGAAATAA AGGT TA CTACC 5′<br>AA T<br>**Target gene**<br>20/22 complementary base pairs<br>Table 2(Lines 7203-7207)<br>Target/seqID:ACADSB/838<br>Nucleic acid seqID/GAM:477/142 | **Page 813, paragraph 1952**<br>"It is yet further appreciated that a function of VGAM142 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM142 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM142 correlate with, and may be deduced from, the identity of the host target genes which VGAM142 binds and inhibits, and the function of these host target genes, as elaborated herein below."<br>Paragraph 5315 per the VGR386 utility (which encodes an `operon-like` cluster of novel viral micro RNA-like gene, including VGAM 142)<br>"It is appreciated that a function of VGR389 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR389 gene include diagnosis, prevention and treatment of viral infection by Vaccinia Virus.Specific functions, and accordingly utilities, of VGR389 gene correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the `operon-like` cluster of VGR389 gene:VGAM142 host target protein, VGAM143 host target protein, VGAM144 host target protein, VGAM145 host target protein,VGAM146 host target protein and VGAM147 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN. The function of these host target genes is elaborated hereinabove with reference to VGAM142, VGAM143, VGAM144, VGAM145, VGAM146 and VGAM147.Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 390(VGR390) viral gene, which encodes an `operon-like` cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art." | | + | | + |

* These sequences are not depicted in Sanger 10.0 database.

[1] TS =TargetScan (version 4.0)
[2] Target conserv. = Target conservation ≥ 2 organisms
[3] mR = miRanda (2003)

# Curriculum Vitae
# Yitzhak Pilpel

## A: Personal Details

**Date of birth**: 12/9/1968
**Place of birth**: Jerusalem, Israel
**Marital status**: Married + 3 children
**Military service**: Four years' service in the IFD
**Citizenship**: Israeli
**Mailing Address**:

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E-mail: pilpel@weizmann.ac.il
Lab home page: http://longitude.weizmann.ac.il

## B: Education

- 2000 - 2002 Postdoctoral Fellow. Department of Genetics, Harvard Medical School, Boston, MA, USA. Advisor: Prof. George M. Church.

- 1995 - 1999 Ph.D. degree. Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel. Thesis title: Structural and evolutionary genomics of molecular recognition repertoires. Advisors: Prof. Doron Lancet; Prof. Ephraim Katchalski-Katzir.

- 1994 - 1995 Studies toward M.Sc. degree; transfer to direct Ph.D. track. Department of Membrane Research and Biophysics, Weizmann Institute of Science, Rehovot, Israel. Advisors: Prof. Doron Lancet; Prof. Ephraim Katchalski-Katzir.

- 1990 - 1993 B.Sc. degree. Major: Biology. Tel-Aviv University, Tel-Aviv, Israel.

## C: Employment History

- 2003 - present Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel. Senior Scientist, group leader.
  Incumbent of the Aser Rothstein Career Development Chair of Genetic Diseases.

## D: Academic Administration

- 2004 - present Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel. Head of the Graduate Program in Bioinformatics.

## E. Other Appointments

**• Positions in academia and membership on committees**

- 2007 - present Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel. Member of the Board of Studies, Life Sciences.
- 2003-present Head Bioinformatics graduate program at the Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel.

**• Teaching experience - courses taught**

- 2003-2006 Developed and taught the course, "Computational Functional Genomics." Feinberg Graduate School, Weizmann Institute of Science.

- 1998 Teaching Assistant for the course, "Programming for Bioinformatics and Internet." Feinberg Graduate School, Weizmann Institute of Science.

- 1997 Lecturer for the course, "Computational Genomic and Bioinformatics." Feinberg Graduate School, Weizmann Institute of Science.

- 1994 Teaching Assistant for the course, "Receptors and Recognition." Feinberg Graduate School, Weizmann Institute of Science.

- 1992 Teaching Assistant in mathematics for the course, "Introduction to Differential and Integral Calculus." Tel Aviv University.

**• Membership on scientific advisory boards, and consulting activities**

- Member of the Program Committee, RECOMB Regulatory Genomics 2006, (San Diego CA, USA).

- Member of the Program Committee, RECOMB 2005, (San Diego CA, USA)

- Member of the Program Committee, RECOMB Regulatory Genomics and Systems Biology 2005, (San Diego CA, USA).

- Member of the Program Committee, RECOMB Regulatory Genomics 2004, (San Diego CA, USA).

- 2001 - 2002 Consultant on modeling and structure prediction of G-protein coupled receptors. Pfizer, Inc., Cambridge. MA, USA.

**• Membership on editorial boards**

- Associate Editor, PLoS Computational Biology

- Associate Editor, Biology Direct

## F: International Recognition

**• Prizes, awards, and competitive scholarships**

- 2007 Levinson Prize in Biology, awarded by the Scientific Council, Weizmann Institute of Science.

- 2006 James Heineman Research Award, (awarded by Minerva Stiftung).

- 2005 EMBO Young Investigator Award, awarded by the European Molecular Biology Organization.

- 2003 Fellowship from the Center for Complexity Sciences – a merit-based fellowship for young Principal Investigators (awarded by the Horowitz Foundation).

- 2002 Fellow of the PhRMA Foundation, a Center for Excellence in Integration of Genomics and Informatics, Harvard University.

- 2000 Fulbright Postdoctoral Award, awarded by the United States - Israel Educational Foundation.

- 1999 Prize of Distinction for outstanding Ph.D. studies. Awarded by the Feinberg Graduate School, Weizmann Institute of Science.

- 1998 First Prize in the National Competition for Multidisciplinary Ph.D. Study. Awarded by the Faculty of Mathematics and Natural Sciences, Hebrew University of Jerusalem.

- 1997 Fellowship of Distinction for outstanding achievement in studies and research. Awarded by the Dean of the Feinberg Graduate School, Weizmann Institute of Science.

**• Invited talks at international meetings**

1. 2007 The German Bioinformatics Conference, Potsdam, Germany.
2. 2007 The 9th International Northern European Bioinformatics Conference, Umeå, Sweden.
3. 2007 "Comparative genomics of translation efficiency." Guest lecturer in the seminar series, Dept. of Biology, Columbia University, New York, NY, USA.
4. 2007 "Comparative genomics of translation efficiency." Guest lecturer in the seminar series, Dept. of Biological Engineering, MIT, Cambridge, MA, USA.
5. 2006 "Differential gene expression regulation and species divergence." International course on "Global interrogations of biological processes," ISREC, Lausanne, Switzerland.

6. 2006 "Differential gene expression regulation and species divergence." Systems Biology and Evolution Workshop, Imperial College, London, UK.

7. 2006 "Coping with genetic and non-genetic stress." Baure Center for Genomics Research, Harvard University, Cambridge, MA, USA.

8. 2006 "Systems biology view of expression regulation." The 6th EMBO Young Investigator Meeting, Vienna, Austria.

9. 2006 "Coping with genetic and non-genetic perturbations." Guest lecturer in the seminar series of the Rockefeller Center for Studies in Physics and Biology, New York, NY, USA.

10. 2005 "Responsive backup circuits." The Yeast Systems Biology Network, Gotenburg, Sweden.

11. 2005 "Coupled sense and anti-sense regulation." The 3rd Bertinoro Computational Biology Meeting, Bertinoro, Italy.

12. 2005 "Transcription control of genetic backup circuits." EMBO Practical Course on Functional Genomics, Milan, Italy.

13. 2004 "Revealing the architecture of genetic backup circuits through inspection of transcription regulatory networks." The First Annual RECOMB Meeting on Regulatory Genomics. University of California at San Diego, San Diego, CA, USA.

14. 2003 "Computational detection and analysis of regulatory SNPs." The 5th International Northern European Bioinformatics Conference, Helsinki, Finland.

15. 2003 "Promoter sequence and the thermodynamics of DNA-protein interactions." The 2nd Annual McGill Workshop on Computational Biology, Barbados.

16. 2001 "Computational identification of genetics regulatory networks." DIMACS Workshop on Integration of Diverse Biological Data, Rutgers University, Piscataway, NJ, USA.

• **Invited talks at national meetings**

1. 2008 "Coping with genetic and non-genetic stress." ILANIT, Eilat, Israel.

2. 2004 "Promoter analysis of gene duplications reveals the architecture of genetic backup circuits." The Annual Meeting of the Israel Society of Genetics, (Haifa, Israel).

3. 2003 "Computational dissections of genetics regulatory networks." The 6th Israeli Bioinformatics Conference, Haifa, Israel.

• **Refereed international conference talks**

1. 2007 "Comparative genomics of translation regulation in yeast," a "Highlight Track" talk. ISMB, (Vienna Austria).

2. 2005 "Genome-wide transcription regulatory circuits controlling cellular malignant transformation." (One of 50 talks selected for oral presentation from 500 submissions. Lecture delivered by my student, since I was unable to attend.) Best Poster Award. ISMB, (Detroit, USA).

3. 2005 "Transcriptional reprogramming in genetic backup circuits." (One of 50 talks selected for oral presentation from 500 submissions. Lecture delivered by my student, since I was unable to attend.) ISMB, (Detroit, USA).

4. 2005 "Characterization of the effects of TF binding site variations on gene expression: Towards predicting the functional outcomes of regulatory SNPs." (Lecture delivered by my student.) RECOMB Regulatory Genomics and Systems Biology, (San Diego, USA).

5. 2005 "Backup by paralogs decouples genes lethality from centrality: evidence for preferential backup of hubs." RECOMB Regulatory Genomics and Systems Biology, (San Diego, USA).

6. 2005 "Phenotypic divergence correlates with translational control signals in protein coding sequences in yeast species." (Lecture delivered by my student.) RECOMB Regulatory Genomics and Systems Biology (San Diego, USA).

## G: Scientific Productivity

• **Competitive national and international grants** (latest grant first)

- 2008 - 2012 "Expression regulatory networks: Beyond promoters and transcription control." European Research Foundation (ERC) "Ideas Grant," a personal competitive grant awarded by the EU. €1,300,000.

- 2004-present A non-competitive grant from the Ben May Foundation. $105,000.

- 2007 - 2009 "Systems biology of regulatory networks." Minerva Foundation. €150,000.

- 2007 - 2008 "A potential role for non-coding RNA in regulating gene expression noise: a mathematical approach" (with T. Tlusty). Clore Center for Biological Physics, Weizmann Institute of Science. $20,000.

- 2006 - 2010 "Evolutionary Conditioning," a non-competitive grant from the Tauber Foundation (with N. Eshel Ben-Jacob, et al.). $200,000.

- 2006 - 2010 James Heineman Research Award, (awarded Minerva Stiftung) €60,000.

- 2006 - 2009 EMBO Young Investigator Award. European Molecular Biology Organization. €45,000.

- 2005 - 2010 "The effect of mutations on transcription regulation." European Union Network of Excellence in Bioinformatics. €300,000.

- 2005 Grant from the Center for Systems Biology, Weizmann Institute of Science. $10,000.

- 2004 - 2007 "Deciphering the structure and logic of genetic regulatory networks and signaling pathways in multi-cellular organisms." Israel Science Foundation. $240,000.

- 2004 - 2006 "Computational dissections of transcription factor-promoter interactions." Minerva Foundation. €75,000

- 2003 - 2004 Personal grant from the Horowitz Foundation Center for Complexity Sciences. $88,000.

**• Students, Postdoctoral and Research Fellows**

- Dr. Itay Furman, 2006 - present. Programmer.

- Dr. Orna Dahan, 2005 - present. Research Fellow.

<u>Postdoctoral Fellows</u>

- Dr. Naomi Siew, 2006 - present. Postdoctoral Fellow (shared with Prof. Dan Tawfik).

- Dr. Maria Rodriguez Martinez, 2006 - present. Postdoctoral Fellow (shared with Dr. Tsvi Tlusty).

Ph.D. Students

- Ran Kafri. 2003 - 2006. Ph.D. student. (Graduated with Distinction on the Dean's List). Currently a postdoctoral fellow with Prof. Marc Kirschner, Harvard Medical School.

- Michal Lapidot, 2003 - present. Ph.D. student. (Recipient of the Horowitz Foundation Center for Complexity Sciences Award).

- Amir Mitchell, 2004 - present. Ph.D. student.

- Reut Shalgi, 2005 - present. Ph.D. student (shared with Moshe Oren). (Recipient of the Horowitz Foundation Center for Complexity Sciences Award. Recipient of the Lee Segal Award of Mathematical Biology Lee Segal Award for Mathematical Applications to Biological Systems).

- Orna Man, 2005 - 2007. Ph.D. student. (Graduated with distinction; Recipient of the Daniel Brenner Memorial Prize, awarded by the Feinberg Graduate School, Weizmann Institute of Science).

- Ilya Venger, 2005 - present. Ph.D. student (shared with Dr. Asaph Aharoni).

- Ophir Shalem, 2007 - present. Ph.D. student

- Zohar Bloom, 2007 - present. Ph.D. student.

M.Sc. Students

- Reut Shalgi, 2003 - 2005. M.Sc. student (shared with Prof. Ron Shamir).

- Yael Garten, 2003 - 2005. M.Sc. student. Currently Ph.D. student, Stanford University.

- Arren-Bar Even, 2004 - 2006. M.Sc. student (shared with Prof. Naama Barkai). (Graduated with Distinction on the Dean's List). Currently working in industry.

- Ilana Lavie, 2004 – 2006. M.Sc. student (shared with Prof. Ronen Basri).

- Ophir Shalem, 2006 – 2007. M.Sc. student (shared with Dr. Eran Segal).

- Avihu Yona, 2007 - present. M.Sc. student.

• **National and international collaborators**

**National:**

- Dr. Asaph Aharoni, Dept. of Plant Sciences, Weizmann Institute of Science
- Prof. Naama Barkai, Dept. of Molecular Genetics, Weizmann Institute of Science
- Prof. Ronen Basri, Dept. of Computer Science and Applied Mathematics, Weizmann Institute of Science
- Prof. Eytan Domany, Dept. of Physics of Complex Systems, Weizmann Institute of Science
- Prof. Moshe Oren, Dept. of Immunology, Weizmann Institute of Science
- Prof. Varda Rotter, Dept. of Molecular Cell Biology, Weizmann Institute of Science
- Dr. Eran Segal, Dept. of Computer Science and Applied Mathematics, Weizmann Institute of Science
- Prof. Dan Tawfik, Dept. of Biological Chemistry, Weizmann Institute of Science

- Prof. Eshel Ben-Jacob, School of Physics and Astronomy, Tel-Aviv University
- Prof. David Horn, School of Physics and Astronomy, Tel-Aviv University
- Prof. Eytan Ruppin, MD, Ph.D., School of Computer Science and School of Medicine, Tel-Aviv University
- Prof. Ron Shamir, School of Computer Science, Tel-Aviv University

**International:**

- Prof. Duccio Cavalieri, Florence University
- Prof. Craig Hunter, Harvard University
- Prof. Roy Kishony, Harvard University
- Prof. Daniel Segre, Boston University

**H: Patents**

Provisionary patent application: "Global and local architecture of the mammalian microRNA-transcription factor regulatory network." In preparation by Yeda Research and Development Co., Ltd.

**I. Languages**

Hebrew: Reading: 3, Writing: 3, Speaking: 3

English: Reading: 3, Writing: 3, Speaking: 3

Scale: 1 (basic) to 3 (fluent)

# List of Publications
# Yitzhak Pilpel

**Refereed Articles**

29. Kafri R, Dahan O, Levy J & **Pilpel Y**. Preferential genetic backup of hubs in the protein interaction network: evidence for evolutionary selection for redundancy. *Proc Natl Acad Sci U S A* (2008, in press).

28. Lapidot M, Man-Mizrahi O, & **Pilpel Y**. Functional characterization of variations within regulatory motifs. *PLoS Genetics* (2008, in press).

27. Segal L,*Lapidot M,* Solan Z, Ruppin E, **Pilpel Y**, & Horn D. Nucleotide variation of regulatory motifs may lead to distinct expression patterns. *Bioinformatics* 2007 23(13):i440-9 (2007). ***These authors contributed equally to the work.**

26. Shalgi R, Leiber D, Oren M. **& Pilpel Y.** Global and local architecture of the mammalian microRNA-transcription factor regulatory network. *PloS. Comput. Biol.* 3(7): e131 (2007).

25. Man O **& Pilpel Y.** Phenotypic divergence of yeast species is associated with differential translational efficiency of entire genetic modules. *Nature Genetics* 39(3): 415-421 (2007).

24. Lapidot M **& Pilpel Y.** Genome wide overview of natural antisense transcription – how is it regulated, how does it regulate. *EMBO report* 7(12): 1216-1222 (2006).

23. Kafri R, Levi M **& Pilpel Y.** The regulatory utilization of genetic redundancy through responsive backup circuits. *Proc Natl Acad Sci U S A* 103(31): 11653-11658 (2006).

22. Xi Y, Shalgi R, Fodstad O, **Pilpel Y**, & Jingfang Ju. Differentially regulated miRNAs and actively translated mRNA transcripts by tumor suppressor p53 in colon cancer. *Clinical Cancer Research* 12(1): 2014-2024 (2006).

21. Bar-Even, A, Paulsson J, Maheshri N, Carmi M, O'Shea E, **Pilpel Y*** & Barkai N.* Noise in protein expression scales with natural protein abundance. *Nature Genetics* 36(6): 36-43 (2006). ***Corresponding authors.**

20. Nadejda S, Vardy E, Molshanski-Mor S, Eitan A, **Pilpel Y**, Schuldiner S, & Bibi E. 3D model of the *Escherichia coli* multidrug transporter MdfA reveals an essential membrane-embedded positive charge. *Biochemistry* 44(45): 14870-14880 (2005).

19. Shalgi R, Lapidot M, Shamir R & **Pilpel Y**. A catalog of stability-associated sequence elements in 3' UTRs of yeast mRNAs. *Genome Biology* 6(10): R86. (2005).

18. Tabach Y, Milyavsky M, Zuk O, Yitzhaki A, Shats I, Domany, E, Rotter,V & **Pilpel Y**. The promoters of human cell cycle genes integrate signals from two tumor suppressive pathways during cellular transformation. *Molecular Systems Biology* 1: 2005.002 (2005).

17. Kafri R, Bar-Even A. & **Pilpel Y**. Transcription control reprogramming in genetic backup circuits. *Nature Genetics* 37(3):295-299 (2005).

16. Garten Y,* Kaplan S* & **Pilpel Y**. Extraction of Transcription Regulatory Signals from Genome-wide DNA-protein interaction Data. *Nucleic Acids Research* 33(2): 605-615 (2005) ***These authors contributed equally to the work.**

15. Lapidot M & **Pilpel Y**. Comprehensive quantitative analyses of the effects of promoter sequence elements on mRNA transcription. *Nucleic Acid Research* 31: 3824-3828 (2003).

14. Sudarsanam P,* **Pilpel Y*** & Church GM. Genome-wide co-occurrence of promoter elements reveals a *cis*-regulatory cassette of rRNA transcription motifs in *S. cerevisiae*. *Genome Research* 12: 1723-1731 (2002). ***These authors contributed equally to the work.**

13. Zhu Z,* **Pilpel, Y*** & Church GM. Identification of transcription factor binding sites via a Transcription Factor-Centric Clustering (TFCC) algorithm. *J.Mol.Biol.* 318: 71-81 (2002). ***These authors contributed equally to the work.**

12. Cohen B, **Pilpel Y**, Mitra R & Church GM. Discrimination between the Yap1p and Yap2p transcriptional networks in yeast. *Mol. Biol. Cell.* 13: 1608-1614 (2002).

11. **Pilpel Y**, Sudarsanam P & Church GM. Identifying regulatory networks by combinatorial analysis of promoter elements. *Nature Genetics* 29: 153-159 (2001).

10. Fuchs T, Glusman G, Horn-Saban S, Lancet D. **& Pilpel Y**. The human olfactory subgenome: from sequence to structure and evolution. *Hum Genet* 108: 1-13 (2001).

9. Lapidot M, **Pilpel Y**, Gilad Y, Falcovitz A, Sharon D, Haaf T. & Lancet D. Mouse-Human Orthology Relationships in an Olfactory Receptor Gene Cluster. *Genomics* 71: 296-306 (2001).

8. Conticello SG, **Pilpel Y**, Glusman G & Fainzilber M. Position-specific codon conservation in hypervariable gene families. *Trends Genet* 16: 57-59 (2000).

7. Glusman G, Bahar A, Sharon D, **Pilpel Y**, White J & Lancet D. The olfactory receptor gene superfamily: data mining, classification, and nomenclature. *Mamm Genome* 11: 1016-1023 (2000).

6. **Pilpel Y**, Ben-Tal N & Lancet D. kPROT: a knowledge-based scale for the propensity of residue orientation in transmembrane segments. Application to membrane protein structure prediction. *J Mol Biol* 294: 921-935 (1999).

5. Sharon D, Glusman G, **Pilpel Y**, Khen M, Gruetzner F, Haaf T. & Lancet D. Primate evolution of an olfactory receptor cluster: diversification by gene conversion and recent emergence of pseudogenes. *Genomics* 61: 24-36 (1999).

4. **Pilpel Y** & Lancet D. The variable and conserved interfaces of modeled olfactory receptor proteins. *Protein Sci* 8: 969-977 (1999).

3. Segre D, Lancet D, Kedem O **& Pilpel Y**. Graded autocatalysis replication domain (GARD): kinetic analysis of self-replication in mutually catalytic sets. *Orig Life Evol Biosph* 28: 501-514 (1998).

2. Segre D, **Pilpel Y** & Lancet D. Mutual catalysis in sets of prebiotic organic molecules: Evolution through computer simulated chemical kinetics. *PhysicaA* 249: 558-564 (1998).

1. Lancet D, Kedem O **& Pilpel Y**. Emergence of order in small autocatalytic sets mantained far from equilibrium: application of a probabilistic receptor affinity distribution (RAD) model. *Ber Bunsenges Phys Chem* 98: 1166-1169 (1994).

**Invited Editorials (News & Views)**

2. Furman I. **& Pilpel Y.** Promoting mining of human promoters. News & Views in *Molecular Systems Biology* 2: 2006.0030 (2006).

1. Pilpel Y & Lancet D. Olfaction. Good reception in fruitfly antennae. News & Views in *Nature* 398: 285-287 (1999).

**Book Chapters**

1. Pilpel, Y, Sosinsky A & Lancet D. Molecular biology of olfactory receptors. *Essays Biochem* 33: 93-104 (1998).

**Invited Reviews**

1. Sharon D, Glusman G, **Pilpel Y**, Horn-Saban S. & Lancet D. Genome dynamics, evolution, and protein modeling in the olfactory receptor gene superfamily. *Ann N Y Acad Sci* 855: 182-193 (1998).

**Refereed Conference Proceedings**

2. Lapidot M **& Pilpel Y.** Characterization of the Effects of TF Binding Site Variations on Gene Expression. Towards Predicting the Functional Outcomes of Regulatory SNPs. *Lecture Notes in Bioinformatics*, LNBI 4023 Proceedings, Springer-Verlag (2007).

1. Man O, Sussman JL **& Pilpel Y.** Examination of the tRNA Adaptation Index as a Predictor of Protein Expression Levels. *Lecture Notes in Bioinformatics*, LNBI 4023 Proceedings, Springer-Verlag (2007).